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April 6, 2005

BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
Room 1061, 5630 Fishers Lane
Rockville, MD 20852

Re: Vitrase® (NDA 21-640)

Dear Sir or Madam:

Enclosed for filing are the original and four copies of a Citizen Petition submitted by ISTA Pharmaceuticals, Inc. concerning marketing exclusivity for Vitrase® (NDA 21-640).

Yours sincerely,

Paul D. Krause for

Marvin J. Garrett,
Vice President, Regulatory Affairs and
Quality Assurance & Compliance
ISTA Pharmaceuticals, Inc.

2005P-0134

CP1

DC: 1748789-1

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CITIZEN PETITION

The undersigned submits this petition on behalf of ISTA Pharmaceuticals, Inc. (ISTA) under section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA) to request that the Commissioner of Food and Drugs restore its original determination of three- rather than five-year exclusivity for Vitrase® (NDA 21-640), a proprietary formulation of highly purified ovine hyaluronidase manufactured by ISTA.

Vitrase was approved in May 2004 for indications including use as a spreading agent to facilitate the absorption and dispersion of other injected drugs. This approval removed hyaluronidase from FDA's "drug shortage" list, where it had been listed since 2001. According to the American Academy of Ophthalmology, prior to 2001 hyaluronidase was widely used in the U.S. during ophthalmic surgery as a spreading agent in conjunction with other drugs.

Vitrase was approved under FDCA section 505(b)(2) based on a reference to FDA's earlier approval of Wydase, a bovine formulation of hyaluronidase (Wyeth Laboratories NDA 06-343), in combination with new clinical investigations conducted by ISTA. In September 2004, FDA granted Vitrase three years of marketing exclusivity. Under the FDCA, three-year exclusivity is available for drug products that contain a previously approved "active ingredient," provided the NDA includes "new clinical investigations . . . essential to approval of the application and conducted or sponsored by the applicant." *See* 21 U.S.C. § 505(j)(5)(D)(iii), (c)(3)(D)(iii). The three-year exclusivity period for Vitrase would have extended until May 5, 2007.

In October 2004, ISTA was informed that FDA was changing its exclusivity determination for Vitrase from three- to five-year exclusivity. *See* Letter From Jonca C. Bull, M.D., FDA CDER ODE V To Marvin J. Garrett, ISTA Pharmaceuticals, Inc. (October 26, 2004) (FDA October 2004 Letter) (Tab A). Under the FDCA, five-year exclusivity is reserved for drug products containing "no active ingredient" that has been previously approved in any other application under [FDCA § 505(b)]." *See* 21 U.S.C. § 505(j)(5)(D)(ii), (c)(3)(D)(ii).

2005P-0134

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In explaining this change in exclusivity, FDA stated that "after reviewing information and data regarding hyaluronidase drug products, which are protein products that have not been fully characterized, the agency has decided that five-year exclusivity is appropriate because we have inadequate information to determine whether any active moiety in Vitrase is the same as any previously approved active moiety." *See* FDA October 2004 Letter.

On March 1, 2005, ISTA met with FDA's Office of Chief Counsel to discuss FDA's decision to change the exclusivity period for Vitrase. Based on that discussion, ISTA submits this Citizen Petition to assert a significant inconsistency between FDA's interpretation of its marketing exclusivity regulations and the governing statute, and to request that FDA restore its original determination of three-year exclusivity for Vitrase.

A. Action Requested

ISTA requests that FDA recognize, consistent with the agency's earlier approval of Vitrase under a 505(b)(2) application referencing FDA's prior finding of safety and efficacy for Wydase (Wyeth Laboratories NDA 06-343), a listed drug product, that Vitrase contains an "active ingredient" that has previously been "approved" within the meaning of the FDCA provisions on marketing exclusivity, and that Vitrase is therefore eligible for three rather than five years of marketing exclusivity.

B. Statement of Grounds

1. In switching Vitrase from three- to five-year marketing exclusivity, FDA applied the regulatory definition "active moiety" in a manner that is inconsistent with the statute.

    a) Statutory provisions on marketing exclusivity and FDA's definition of the term "active moiety."

Under the FDCA, a drug manufacturer is eligible for three years of marketing exclusivity if his section 505(b) application includes an "active ingredient (including any ester or salt of the active ingredient)" that "has been approved in another [section 505(b)] application," and if the manufacturer's application contains reports of "new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." *See* 21 U.S.C. § 355(c)(3)(D)(iii), (j)(4)(d)(iii). Five years of exclusivity are available if the product contains "no active ingredient (including any ester or salt of the active ingredient)" that "has been approved in any other [section 505(b)] application." *Id.* § 355(c)(3)(D)(ii), (j)(4)(d)(ii). These marketing exclusivity provisions were added to the FDCA in 1984 as part of the Hatch-Waxman amendments.

In proposing its regulations on marketing exclusivity, FDA took account of a potential ambiguity in the statutory phrase "no active ingredient (including any ester or salt of the active ingredient)."[1] In order to resolve this ambiguity and to ensure that five-year exclusivity did not become available to "minor variations of previously approved chemical compounds," *see* 54 Fed. Reg. 28,872, 28,898 (July 10, 1989) (proposed rule), FDA by regulation reserved five-year exclusivity to "new chemical entities" -- defined as drugs that contain "no active moiety that has been approved by FDA in any other application submitted under [FDCA section 505(b)]." *See* 21 C.F.R. § 314.108(a). "Active moiety" was in turn defined as "the molecule or ion," excluding those appended portions of the molecule "that cause the drug to be an ester, salt . . . or other noncovalent derivative" of the molecule, that is "responsible for the physiological or pharmacological action of the drug substance." *See id.* § 314.108(a).[2]

By defining "active moiety" to exclude "those appended portions of the molecule that cause the drug to be an ester, salt . . . or other noncovalent derivative," FDA was able to propose regulations limiting five-year eligibility to more innovative products. *See* 54 Fed. Reg. 28,872, 28,898. The agency's desired result, as stated in its explanation for the proposed "active moiety" definition, was to ensure that "[a] drug product will . . . not be considered a 'new chemical entity' entitled to five years of exclusivity if it contains a previously approved active moiety, even if the particular ester or salt . . . or other noncovalent derivative [in the subsequent application] has not been previously approved." *See id.* Under FDA's proposed interpretation, a previously approved chemical drug and its subsequently submitted salt would have

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1 *See* 54 Fed. Reg. 28,872, 28,898 (July 10, 1989) (explaining proposed definition of "active moiety"). For example, if the "active ingredient" in the statutory parenthetical refers to the original product, then a subsequent applicant seeking approval for a salt of a previously approved product would not be entitled to five years of exclusivity. If, however, the "active ingredient" in the parenthetical is read to refer to the subsequent (rather than the original) applicant, the statute could be read to grant five years of exclusivity to a product whose active ingredient was merely the salt of a previously approved product -- hardly a significant innovation. An interpretation very similar to this was urged by the plaintiff (later appellant) manufacturer in *Abbott Laboratories v. Young*, 920 F.2d 984 (D.C. Cir. 1990), *cert. denied*, 502 U.S. 819 (1991). The district court proceedings in *Abbott* took place during 1988, four years after the enactment of Hatch-Waxman and one year before FDA issued its proposed regulations on marketing exclusivity. *See Abbott Laboratories v. Young*, 691 F.Supp. 462 (D.D.C. 1988).

2 Neither the term "new chemical entity" nor the term "active moiety" appears in the statute. In the preamble to the proposed rule, FDA indicated that the "new chemical entity" designation was based on the "new molecular entity" or "Type 1" classification used internally by FDA at the time of the Hatch-Waxman amendments to classify incoming drug applications. *See* 54 Fed. Reg. 28,872, 28,897-98.

different "active ingredients" in the statutory sense, but would contain the same "active moiety" under FDA regulations -- so that the subsequently submitted salt would be ineligible for five-year exclusivity.[3]

In the final rule, FDA adopted its proposed definition of "active moiety" without change.[4] *See* 59 Fed. Reg. 50,338, 50,357, 50,368 (October 3, 1994). The agency further concluded that "the term 'active ingredient,'" as used in the statute, "means active moiety." *Id.* at 50,358.

b) FDA's interpretation of "active moiety" in the Vitrase case is inconsistent with the statute, which assigns three-year exclusivity to products whose "active ingredient" has been approved in a specific past case.

FDA's stated rationale in switching Vitrase to five-year exclusivity was given as follows: "[A]fter reviewing information and data regarding hyaluronidase drug products, which are protein products that have not been fully characterized, the agency has decided that five-year exclusivity is appropriate because we have inadequate information to determine *whether any active moiety in Vitrase® is the same as any previously approved active moiety*." *See* FDA October 2004 Letter (emphasis added).

The agency's reasoning appears to be based on the premise that the molecular structure of hyaluronidase products has not been fully characterized. Applying the terms of the "active moiety" definition, FDA next appears to conclude that the "molecule . . . responsible for the physiological or pharmacological action of [Vitrase]" cannot be fully identified. As a consequence (under FDA's analysis), the agency cannot determine whether any "active moiety" in Vitrase is the same as any "active moiety" that has previously been approved for marketing. Therefore, Vitrase

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[3] This interpretation, as applied in the small-molecule scenario involving a salt of a previously-approved product, is consistent with the D.C. Circuit ruling in *Abbott*, which was issued subsequent to the close of the comment period on FDA's proposed marketing exclusivity regulations. The *Abbott* court rejected the manufacturer's interpretation of the statutory phrase "active ingredient (including any ester or salt of the active ingredient)," whereby the salt of a previously approved active ingredient would have been eligible for the longer of two exclusivity periods. *See Abbott Laboratories*, 920 F.2d 984, 988. The court also found the phrase "active ingredient (including any ester or salt of the active ingredient)" ambiguous, and remanded to the district court with instructions to remand to the agency. *Id.* at 987-990.

[4] In issuing its final rule, FDA interpreted the *Abbott* appeal ruling and remand as consistent with the proposed definition of "active moiety." *See* 59 Fed. Reg. 50,338, 50,358 (October 3, 1994).

is a "new chemical entity" and only five-year exclusivity can be granted. *See* 21 C.F.R. § 314.108(b)(2).

In switching Vitrase from three- to five-year exclusivity, FDA has interpreted "active moiety" to mean something unidentified and possibly indeterminate -- an ingredient whose approval status cannot be known. Under this interpretation, FDA is essentially denying three-year exclusivity because of the possibility that something indeterminate -- the "active moiety" in Vitrase -- may not have been previously approved.

This interpretation of the term "active moiety" is inconsistent with the statutory provisions on marketing exclusivity. Under the FDCA, three-year exclusivity is assigned to drugs whose "active ingredient" has been previously "approved" in another section 505(b) application. *See* 21 U.S.C. § 355(c)(3)(D)(iii), (j)(4)(d)(iii). This statutory criterion is based on two terms, neither of which is ambiguous. First, while the term "active ingredient" is not defined in the statute, it has been consistently understood from the time of enactment to mean a therapeutically active component of a finished drug product.[5] Nor is the statute's reference to a drug's being previously "approved" in any way ambiguous. An "approved" active ingredient is a drug component that has been evaluated by FDA for safety, efficacy, and manufacturing controls in the context of a particular application, and has been approved for sale as part of a finished drug product.

ISTA does not dispute the difficulty, as a scientific matter, of characterizing hyaluronidase products at the molecular level. For purposes of the marketing exclusivity analysis under FDCA section 505, however, this difficulty in characterization does not determine the outcome. The exclusivity analysis must be

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[5] FDA statements contemporaneous with the enactment of Hatch-Waxman support this understanding of the term. In issuing its 1985 final rule containing the NDA regulations, for example, FDA cited the definition of "active ingredient" used in its "current good manufacturing [CGMP] regulations," *see* 50 Fed. Reg. 7451, 7457 (February 22, 1985), to justify the scope of its proposed definition of "drug substance." Specifically, FDA stated that its proposed definition of "drug substance" was consistent with the definition of "active ingredient" in the CGMP regulations: "any component" that is "intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals." *See* 43 Fed. Reg. 45,013, 45,077 (September 29, 1978) (final rule notice for CGMP regulations). This CGMP definition of "active ingredient," which remains the same today, clearly refers to a component of a finished drug product. 21 C.F.R. § 210.3(b)(7). At the time of the Hatch-Waxman Amendments, therefore, the term "active ingredient" was recognized generally, and by FDA in particular, to mean an ingredient in a finished drug product.

consistent with the statute, which assigns three-year exclusivity to a product whose "active ingredient" has been previously approved in an application for marketing.[6] FDA's interpretation of the Vitrase "active moiety" as an unidentified ingredient, whose previous-approval status cannot be determined, is at odds with this statutory criterion, and FDA's resulting denial of three-year exclusivity to Vitrase conflicts with the statute. FDA's interpretation also contradicts its own statement that "active moiety" has the same meaning as "active ingredient." *See* 59 Fed. Reg. 50,338, 50,357 (preamble to final rule on marketing exclusivity regulations).

As discussed above in Section 1(a), the phrase "active ingredient (including any ester or salt of the active ingredient)" in the marketing exclusivity provisions of the FDCA is potentially ambiguous. To the extent FDA applies the term "active moiety" to resolve this ambiguity and to address a question left open by Congress, the agency's interpretation is entitled to deference. *See Chevron U.S.A. Inc. v. National Resources Defense Council, Inc.*, 467 U.S. 837, 842-43 (1984). Here, however, the statute is unambiguous in its reference to a previously approved "active ingredient," meaning a component of a drug product that can be tested by a sponsor and approved by FDA. FDA has no basis to interpret the term otherwise.[7]

2. When the Vitrase exclusivity analysis is made consistent with statutory criteria, Vitrase receives three-year exclusivity and is protected against all applications for the same "conditions of approval."

   a) FDA's 2004 approval of Vitrase under FDCA section 505(b)(2) was a determination that Vitrase's "active ingredient" had been previously approved.

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[6] As discussed in Section 2(a), this criterion is satisfied for Vitrase because Vitrase's active ingredient was previously approved in the Wydase application.

[7] *Abbott* provides no basis for FDA to assert that the term "active ingredient" is itself ambiguous, or that the meaning of an active ingredient being previously "approved" by FDA is in any way ambiguous. The ambiguity that was identified by the *Abbott* court, and that led to the court's remand to FDA, arose from the repetition of the term "active ingredient" in the parenthetical phrase "including any ester or salt of the active ingredient" -- *i.e.*, the statute is ambiguous as to whether the parenthetical might refer to the second of two products (in which case the salt of a previously approved active ingredient could be awarded five-year exclusivity). This particular issue was at stake in *Abbott* because the manufacturer sought the longer of two exclusivity periods for the salt of a previously approved product. *See Abbott*, 920 F.2d 984, 989.

Under the statutory criteria for marketing exclusivity discussed in the previous section, and as FDA has recognized, the determination that two drugs have the same "active ingredient" must be made "on a case-by-case basis." *See* 54 Fed. Reg. 28,872, 28,898.[8] Therefore, three-year exclusivity will be appropriate where a drug's "active ingredient" has previously been approved in a specific past case.

In August 2003, ISTA submitted NDA 21-640 under FDCA section 505(b)(2), seeking approval of Vitrase ovine hyaluronidase as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. *See* Letter From Marvin J. Garrett, ISTA To Wiley Chambers, M.D., FDA CDER (August 4, 2003) (Tab B), at 1. ISTA sought to rely on FDA's previous findings of safety and efficacy for Wydase, a bovine formulation of hyaluronidase (Wyeth Laboratories NDA 06-343). *See id.* As ISTA stated in its application, "[t]he Vitrase formulation differs from the Wydase formulation only in that it is of ovine origin and is preservative-free." *Id.*

FDA has recognized section 505(b)(2) as an appropriate vehicle for approval of a drug product that "contain[s] an active ingredient(s) derived from animal or botanical sources or recombinant technology" and where the clinical investigations required for approval "are necessary to show *that the active ingredient is the same as an active ingredient in a listed drug*." *See* FDA Draft Guidance, *Applications Covered By Section 505(b)(2)* (October 1999) (FDA 505(b)(2) Guidance) (emphasis added), at 4.

When FDA approved ISTA's Vitrase NDA 21-640 under section 505(b)(2), FDA relied on its previous finding of safety and efficacy for Wydase, in combination with additional data submitted by ISTA, to determine that the active ingredient in

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[8] Consistent with those statutory provisions, FDA cannot assume that all products that fall within the USP monograph for hyaluronidase have the same "active ingredient" for purposes of determining three- and five-year exclusivity. For example, while two products from different "mammalian" testicular sources could both fall within the USP monograph, *see* USP Official Monographs, Hyaluronidase Injection and Hyaluronidase for Injection, USP 28 NF 23 (January 1, 2005), that would not be sufficient on its own to establish that the two products had the same active ingredient. Under FDA guidance, assuming further clinical investigations were necessary, a section 505(b)(2) application would still be necessary to show that the two products had the same active ingredient. *See* FDA Draft Guidance, *Applications Covered By Section 505(b)(2)* (October 1999), at 4 (example involving 505(b)(2) applications for products from animal sources); *see also* Letter From Steven Galson, FDA CDER to Kent S. Allenby, Baxter Healthcare Corp. (May 5, 2004) (FDA Docket No. 2003P-0494/CP1), at 6-7 (clinical safety investigations required in marketing applications for hyaluronidase products).

Vitrase was the same as the active ingredient in Wydase. FDA reached this determination -- that the two active ingredients were the same -- despite the fact that, as detailed in the Vitrase NDA, "[t]he exact chemical structure" of both the Vitrase and Wydase enzymes were "unknown." *See* Vitrase NDA 21-640, Section 2.2 (Comparison of Draft Vitrase and Approved Wydase Labeling), at 10 (August 4, 2003) (Tab B). FDA also recognized the uncharacterized nature of the hyaluronidase molecule in its response (issued the same month Vitrase was approved) to the Citizen Petition filed by Baxter Healthcare. *See* Letter From Steven Galson, FDA CDER to Kent S. Allenby, Baxter Healthcare Corp. (May 5, 2004) (FDA Docket No. 2003P-0494/CP1) (FDA Baxter Response) (Tab C), at 2 ("naturally occurring hyaluronidases have never been fully characterized with respect to chemical structure and impurities").

Applying the statutory criterion that three-year exclusivity is awarded to a product whose "active ingredient" has been previously approved, therefore, Vitrase clearly qualifies for three- rather than five-year exclusivity.

b) Under a grant of three-year exclusivity, Vitrase is protected against any ANDAs or 505(b)(2) applications that seek approval of the same active ingredient for Vitrase's approved indication.

Under the statutory provisions governing marketing exclusivity, a grant of three-year exclusivity prevents FDA from making effective the approval of any abbreviated new drug application (ANDA) or 505(b)(2) application for the same "conditions of approval" as the application to which exclusivity was awarded. *See* 21 U.S.C. § 355(c)(3)(D)(iii), (j)(4)(d)(iii). FDA regulations contain a similar provision. *See* 21 C.F.R. § 314.108(b)(4)(iv) (three-year exclusivity prevents FDA making effective the approval of any ANDA or 505(b)(2) application "for the conditions of approval of the original application").

Therefore, if Vitrase is granted three-year exclusivity, Vitrase is protected for three years against the approval of any ANDA or 505(b)(2) for the same "conditions of approval" -- that is, against any application that purports to contain the same active ingredient (hyaluronidase) and that seeks approval for the same indications as Vitrase.[9]

This interpretation is supported by FDA statements in the preamble to the agency's final rules on marketing exclusivity. Having proposed regulations in which

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[9] Vitrase's three-year exclusivity should have prevented FDA from making effective the approval of the Amphastar NDA, which was submitted to FDA prior to the Vitrase approval.

three-year exclusivity would protect the holder against any ANDA or 505(b)(2) for the "conditions of approval" associated with the original drug, the agency received a comment asking that FDA "interpret the phrase 'conditions of approval' . . . *narrowly* to limit exclusivity to studies conducted by the applicant." *See* 59 Fed. Reg. 50,338, 50,359 (comment 105) (emphasis added). The comment requested an interpretation whereby "subsequent applicants who conduct their own studies to obtain approval [would] not be subject to the original applicant's exclusivity." *See id.* at 50,360.

FDA declined to adopt this proposed limitation on the meaning of "conditions of approval." While acknowledging that three-year exclusivity does not protect the holder against approval of a full NDA involving the same active ingredient and the same indications, the agency rejected the interpretation that three-year exclusivity could be overcome by a subsequent applicant who simply conducted new studies (or otherwise obtained the right to submit new studies, for example by providing more than 50 per cent of the funding). *See id.* To the extent a subsequent applicant submits new clinical investigations while seeking approval for the same "conditions of approval" as the exclusivity holder, therefore, that applicant's approval cannot be made effective for three years after the holder's approval date. *See also* 54 Fed. Reg. 28,872, 28,899 (three-year exclusivity blocks the approval of "an ANDA or of a 505(b)(2) application for a duplicate drug product").

3. Consequences of five-year exclusivity for Vitrase illustrate the tension between FDA's regulatory interpretation and the governing statute.

The practical consequence of FDA's current interpretation of "active moiety," as discussed above in Section 1(b), is that any new hyaluronidase product submitted for approval is likely to be granted "new chemical entity" status and five-year exclusivity. To the extent these competing exclusivities are granted, they are likely to give rise to considerable confusion. In addition, the competing exclusivity scenario further illustrates the inconsistencies arising in the Vitrase case between FDA's interpretation of its regulations and the requirements of the governing statute.

Assuming five-year exclusivity is retained for Vitrase, that exclusivity would block the submission of any ANDA or 505(b)(2) application containing the same "active moiety." *See* 21 C.F.R. § 314.108(b)(2). Under FDA's current interpretation -- *i.e.*, that the agency cannot determine whether any "active moiety" in a hyaluronidase product is the same as one that has been previously approved -- Vitrase's exclusivity would be unlikely to block the submission of subsequent hyaluronidase applications.

Therefore, FDA is likely to receive applications for subsequent hyaluronidase products. These subsequent applications cannot be approved as ANDAs under FDCA section 505(j), because the applicant's active ingredient would not be "the same as" that of the listed drug. *See* 21 U.S.C. § 355(j)(2)(A). Consistent with FDA regulation

and guidance, subsequent applicants would be seeking a "change" relative to previously approved products and would at a minimum be required to submit a 505(b)(2) application including new clinical studies. *See* 21 C.F.R. § 314.54(a); FDA 505(b)(2) Guidance at 3. Depending on the nature of the product and the scope of the studies required, a full application under section 505(b)(1) might be necessary for marketing approval.[10]

Under FDA's current interpretation of the regulations, each new hyaluronidase product would, like Vitrase, be a "new chemical entity" entitled to its own five-year exclusivity period. Each sponsor would therefore be entitled to protection against subsequent applications containing the same "active moiety" -- but to the extent it remains impossible for FDA to determine whether any two hyaluronidase products contain the same "active moiety," these various exclusivity periods will either be meaningless or (more likely) a source of ongoing dispute.

This scenario, in which FDA prospectively classifies all hyaluronidase products as "new chemical entities," provides a further illustration of how FDA's current application of the marketing exclusivity regulations is inconsistent with the governing statute. As discussed in Section 1(b) above, the statutory grant of marketing exclusivity depends on whether a product's "active ingredient" -- a component of a drug product that can be evaluated for marketing approval -- has in fact been "approved" in a specific past case. This statutory criterion does not leave FDA the discretion to prospectively determine the exclusivity status of certain categories of drugs[11] -- as FDA here intends to classify all hyaluronidase products as "new chemical entities" eligible for five-year exclusivity.

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[10] FDA has indicated in guidance that an application for a product "derived from animal or botanical sources or recombinant technology" may be appropriately submitted for approval under section 505(b)(2) where additional clinical studies are necessary. FDA 505(b)(2) Guidance at 5. As FDA has further indicated in its response to the Baxter petition, the minimum 505(b)(2) submission for such products would involve the submission of additional clinical data for safety purposes. *See* FDA Baxter Response at 6-7. New clinical investigations on efficacy may not be required if the product falls within the USP monograph and can be tested with the USP *in vitro* assay. *See id.* at 3-4. For products that fall outside the USP monograph, however, such as those produced using recombinant technologies, additional efficacy data should be required in addition to safety studies.

[11] As noted above in Section 1(a), FDA has indicated that the term "new chemical entity" was based on the "new molecular entity" or "Type 1" designation that was part of an internal classification system FDA was using at the time of the Hatch-Waxman amendments. *See* 54 Fed. Reg. 28,872, 28,897-98 (proposed rule on marketing exclusivity regulations). This internal classification system was used by FDA to "identify promising drugs" among incoming applications and to prioritize agency use of resources. *See* 47 Fed. Reg. 46,622, 46,625 (October 19, 1982) (continued...)

C. Environmental Impact

This petition is categorically exempt from the requirement for an environmental assessment or an environmental impact statement pursuant to 21 C.F.R. §§ 25.30 and 25.31.

D. Economic Impact

Information on the economic impact of the petition will be provided upon request.

E. Certification

The undersigned certifies that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Respectfully submitted,

Paul D. Krause for

Marvin J. Garrett,
Vice President, Regulatory Affairs and
Quality Assurance & Compliance
ISTA Pharmaceuticals, Inc.

(proposed rule on NDA regulations). The regulatory designation "new chemical entity," however, cannot be made equivalent to the term "new molecular entity" as previously used by FDA for internal purposes. "New chemical entity," as a regulatory term used to implement FDCA provisions on marketing exclusivity, must be applied in a manner consistent with the statute -- which requires that exclusivity be granted through an examination of past approvals relevant to a particular "active ingredient," rather than by means of a prospective designation applicable to certain categories of drugs.